Acute Renal Failure Due to a Bismuth Preparation

JOHN A. JAMES., M.B., *Los Angeles*

IT IS WELL KNOWN that the salts of bismuth are toxic to the kidney. It may be less widely known that oral preparations containing soluble bismuth salts are still available on prescription, and that these may cause serious damage in doses which are not greatly in excess of those recommended by the manufacturer for therapeutic use. The following report describes such an occurrence.

Report of a Case

The patient, a 14-year-old girl, became ill with a cold, sore throat and a dry non-productive cough 17 days before admission to hospital. After five days of illness she was seen by a physician, who diagnosed bronchitis and prescribed oral penicillin. At approximately the same time (12 days before admission to hospital) "7 or 8 pain pills" were given to her by a sympathetic friend for whom they had been prescribed as treatment for sore throat. The patient took all of them over a period of a few hours. They were later identified as bismuth sodium triglycollamate (Bistrimate®), each tablet containing 75 mg of elemental bismuth.

Shortly after taking the pills the patient began to vomit. Vomiting occurred two or three times daily despite treatment with anti-emetics, and she became very tired and weak. Although her urine output decreased, there was no defined period of anuria. No abdominal pain or skin rash was noted at any time. She was transferred to the Los Angeles County-University of Southern California Medical Center when it was determined that she had blood urea nitrogen (BUN) in excess of 150 mg per 100 ml and serum creatinine of 18 mg per 100 ml.

There was no previous history suggesting underlying renal disease. The patient had experienced seizures during the neonatal period and three episodes of seizures occurred subsequently, the last at four years of age. She was treated with anti-convulsants until she was ten years of age. Apart from some emotional instability, probably related to a difficult home situation, her health was good.

On physical examination the patient was observed to be lethargic but not in acute distress. There was no edema. Body weight on admission was 111 pounds and blood pressure was 125/65 mm of mercury. The mouth was dry, but there was no ulceration or pigmentation. No skin rash was detected other than moderate acne vulgaris. She complained of some numbness of the feet and a questionable loss of sensation to light touch was detected over the soles.

Hemoglobin was 12.1 gm per 100 ml of blood, leukocytes 5800 per cu mm, BUN 177 mg per 100 ml, serum sodium 128 mEq, potassium 4.3 mEq and bicarbonate 15 mEq per liter, sugar 120 mg, creatinine 24 mg and uric acid 15.6 mg per 100 ml, albumin 3.5 gm and globulin 3.7 gm per 100 ml and cholesterol 143 mg per 100 ml. No Beta-hemolytic streptococci grew on culture of material from the throat. The antistreptolysin titer was 100 Todd units. No bismuth was detected in a specimen of serum submitted two days after admission. Urinalysis showed specific gravity 1008, 1+ pro-

From the Pediatric Inpatient Service, Los Angeles County-University of Southern California Medical Center, and the Department of Pediatrics, University of Southern California School of Medicine, Los Angeles.

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Reprint requests to: Los Angeles County General Hospital, 1200 North State Street, Los Angeles 90033.

tein, and a positive reaction for glucose; there were 2 to 5 leukocytes and 1 to 2 erythrocytes per high-power field. No casts were seen. A renal scan using I-131 hippuran showed that both kidneys were of normal size but that there was delayed concentration and excretion of the test material.

Clinical Course

Administration of intravenous fluids without potassium was begun to replace the fluid losses resulting from persistent vomiting. In view of the generally good condition of the patient and the absence of hyperkalemia or severe acidosis, it was decided not to undertake dialysis immediately. She was not treated with demercaprol (BAL) because of the long interval which had elapsed between the ingestion of bismuth and her admission to the hospital. She voided urine only once during the first 16 hours after admission, but during the succeeding three days the urine output rose to 3500 ml daily. The daily output, body weight and BUN determinations are shown in Chart 1. Daily urinalysis continued to show 1+ protein and positive reactions for glucose. The blood sugar remained within normal limits throughout. The patient was discharged on the tenth hospital day in good spirits and eating well.

At follow-up examination three weeks later, she had no complaints and no physical abnormalities were noted. The blood pressure was 104/62 mm of mercury. Body weight was 109 pounds. BUN was 17 mg per 100 ml. One week later, the BUN was 16 mg and serum creatinine 0.9 mg per 100 ml, and the 24-hour creatinine clearance was 160 liters per 1.73 square meters of body surface area. Protein excretion in the urine was less than 0.1 gram in 24 hours. A routine urine specimen was negative for protein and glucose and an intravenous pyelogram showed no abnormality.

Discussion

The medicinal use of bismuth preparations dates from 1785 and until the introduction of penicillin in the 1940s, combined therapy with arsenicals and bismuth was a standard treatment for syphilis. This combination of drugs is still used in the treatment of amebiasis, and bismuth therapy is still advocated in some texts for the treatment of verrucae, condylomata acuminata and some kinds of chronic dermatosis such as lichen planus, scleroderma and discoid lupus. However, controlled studies of the value of bismuth therapy in skin

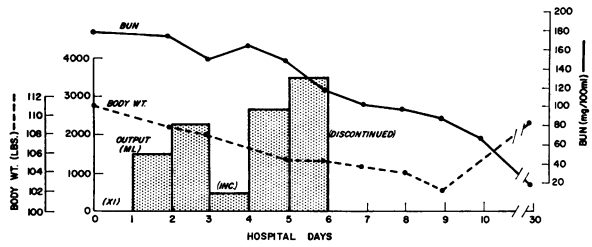

Chart 1.—Urine output, body weight and blood urea nitrogen determinations for patient who had taken "overdose" of bismuth preparation.

disorders are hard to find. Insoluble bismuth salts such as the sub-carbonate are still used for the symptomatic treatment of diarrhea and in protective creams and pastes.[1] The bismuth is non-toxic in this form, although the subnitrate salt may cause methemoglobinemia.

Soluble bismuth salts have both acute and chronic toxicity, although cases of poisoning have become increasingly uncommon as the indications for bismuth therapy have diminished. The symptoms of acute poisoning include vomiting, skin rashes (the erythema of the 9th day) oliguria or anuria, jaundice and stomatitis.[1,2,3] Symptoms of more chronic toxicity include a bismuth line on the gums, pigmentation of the soft palate and cheeks and, rarely, of the skin (bismuthia). Peripheral neuritis is a rare manifestation. A bismuth line of increased density may be seen radiographically at the growing ends of the long bones in children.

Ninety percent of absorbed bismuth is excreted through the kidneys, and acute parenchymal renal failure with oliguria is the most severe manifestation of bismuth nephrotoxicity.[2,3,4,5] In less severe cases there may be a moderate increase in the BUN, proteinuria and a Fanconi syndrome with glycosuria, phosphaturia and aminoaciduria.[6] Proteinuria and glycosuria were observed in the present case. The nature of the physiologic disturbances that have been reported, as well as the microscopic findings at autopsy, suggest that the principal site of injury is the proximal tubule. Distinctive intranuclear and intracytoplasmic inclusions are commonly found within the proximal tubular cells at autopsy in cases of chronic bismuth intoxication.[7,8] The nature of the renal injury due to bismuth is unknown but, like mercury, bismuth may inactivate the sulfhydryl groups necessary for active tubular transport processes.

The sequence of events in the present case, namely persistent vomiting and lethargy, followed by the development of acute renal failure, is typi-

cal of acute bismuth toxicity. We have no reason to believe that the patient took more than 525 to 600 mg of bismuth ("7 or 8 pills" of 75 mg each) although no other means of verifying her account of the incident is available to us. The manufacturer of Bistrimate* recommends a dose of one or two tablets three times daily for seven to ten days for treatment of "chronic sore throat." Accordingly, the dose taken by the patient over a period of a few hours was about three times the recommended daily adult dose. There was no evidence, either from the history or from the renal function studies performed after recovery, that the patient had any preexisting renal disease.

Urizar and Vernier[5] recently were able to collect reports of 30 cases of fatal and non-fatal bismuth nephrotoxicity in children from the literature over the past 25 years. In most cases the bismuth had been given by injection for the treatment of stomatitis or warts. Since there is little evidence that bismuth is of any therapeutic value in these disorders, and since bismuth therapy for other diseases has become obsolete, there seems no good reason why bismuth preparations should continue to be marketed. Certainly physicians and patients may reasonably expect that preparations offered for the symptomatic treatment of sore throat will be free from serious toxicity, even should the recommended dose be substantially exceeded.

Summary

A case of acute renal failure in a 14-year-old girl due to an oral bismuth preparation is reported. The dose ingested by the patient—not on medical advice—was approximately three times the daily dose recommended by the manufacturer for the treatment of "chronic sore throat." It is difficult to find any justification for the continued use of such preparations.

*Smith, Miller and Patch, Inc., New York.

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Carotenemia Associated With Papaya Ingestion

DAVID J. COSTANZA, M.D., *San Rafael*

CAROTENEMIA, a well known entity, was first described by Hess and Myers in 1919.[1] The clinical yellowness of the skin is due to the deposit of beta carotene in the fat-soluble stratum cornium. The condition is noted more in areas having a thick cornium (for example, the soles and palms) than in areas without cornium (mucosa, submucosa and subconjunctivae). Carotenemia occurs in cases of excessive ingestion of certain fruits and vegetables as well as in patients with nephrosis, diabetes and hypothyroidism, and it has been associated with myxedema.[2]

Fruits and vegetables containing quantities of carotene are carrots, squash, oranges, yellow corn, apple juice, butter, eggs, yellow beans, kale, rutabagas, yellow squash, pumpkins, yellow turnips, sweet potatoes, peaches, apricots, parsnips and papayas. Hughes and Wooten[3] reported that farmers have learned to feed carrots and pumpkins to dairy cows in winter months so that the butter made from their milk will be a deeper yellow than that which results from hay feedings.

Other causes of a yellowish-red to orange hue of the skin have been reported. In 1960 lycopenemia associated with excessive ingestion of tomato juice was described by Reich, Schwachman and Craig;[4] they found a yellowish discoloration of the skin and concentration of lycopene in the serum and liver. In 1966 Hughes and Wooten[3] reported two patients with orange-colored skin, owing in one case to ingestion of carrots, yellow squash, rutabagas and tomato juice, and in the other to carrots and tomatoes.

In the case reported herein excessive ingestion of papayas caused clinical carotenemia, which

From the Medical Services, San Francisco General Hospital, and the Department of Medicine, University of California School of Medicine, San Francisco.

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Reprint requests to: 710 C Street, San Rafael 94901.